

General

Guideline Title

Guidelines for the management of cerebral cavernous malformations in adults.

Bibliographic Source(s)

Samarasekera N, Poorthuis M, Kontoh K, Stuart I, Respinger C, Berg J, Kitchen N, Salman RA. Guidelines for the management of cerebral cavernous malformations in adults. London (England): Cavernoma Alliance UK, Genetic Alliance UK; 2012. 42 p. [227 references]

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Diagnostic Guidelines

The guideline authors recommend that brain magnetic resonance imaging (MRI) using T1-weighted, T2-weighted, and hemosiderin-sensitive sequences should be performed to: (a) investigate patients with brain masses accompanied by vasogenic oedema and substantial amounts of blood, (b) diagnose cerebral cavernous malformations (CCM) and (c) determine whether CCM are solitary or multiple. Reference should be made to CCM diagnostic criteria and definitions and reporting standards for CCM hemorrhage (Rigamonti et al., 1987; Al-Shahi Salman et al., 2008).

Therapeutic Guidelines

How Should an Adult with an Incidentally Discovered CCM Be Managed?

The guideline authors recommend that decisions about the treatment of adults with incidentally-discovered CCM be made on a case-by-case basis, given the absence of randomized trials or observational studies with dramatic effects specific to these adults.

How Should an Adult with a CCM That Has Caused One Intracerebral Hemorrhage (ICH) or Focal Neurological Deficit (FND) Be Managed?

The guideline authors recommend that decisions about the treatment of adults with CCM that have already caused one ICH or FND be made on a case-by-case basis, given the absence of randomized trials or observational studies with dramatic effects specific to these adults.

How Should an Adult with a CCM That Has Caused More Than One ICH or FND Be Managed?

The guideline authors recommend that decisions about the treatment of adults with CCM that have caused more than one ICH or FND be made

on a case-by-case basis, given the absence of randomized trials or observational studies with dramatic effects specific to these adults.

How Should an Adult with a CCM That Has Caused Epileptic Seizure(s) Be Managed?

The guideline authors recommend adherence to existing guidelines for the management of first seizures and epilepsy in general (Scottish Intercollegiate Guidelines Network [SIGN], 2005; National Institute for Health and Clinical Excellence [NICE], 2012), given the absence of randomized trials or observational studies with dramatic effects for adults with a CCM that has caused a first seizure or epilepsy.

How Should CCM Be Managed in Mothers Before, During, and After Birth?

The guideline authors recommend that decisions about the treatment of mothers with CCM be made on a case-by-case basis, given the absence of randomized trials or observational studies with dramatic effects specific to these women.

Should the Existence of a CCM Influence the Prescription of Antithrombotic or Thrombolytic Medications?

The guideline authors recommend that decisions about antithrombotic or thrombolytic treatment of adults with CCM be made on a case-by-case basis, given the absence of randomized trials or observational studies with dramatic effects specific to these adults. The authors recommend that clinicians bear in mind the beneficial effects of antithrombotic and thrombolytic drugs shown for some vaso-occlusive diseases in randomized controlled trials, which will have included some adults with CCM.

Genetic Guidelines

What Is the Likelihood of Finding a Mutation in the CCM1, CCM2 or CCM3 Genes?

The guideline authors do not recommend mutation analysis in the CCM 1, 2, and 3 genes for adults without a family history and only one CCM on hemosiderin-sensitive brain MRI sequences. They recommend that mutation analysis be considered by adults with CCM(s) and a family history of CCM, and by adults with multiple CCM and no family history.

Other Guidelines

Which Professional Groups Should Manage Adults with CCMs?

The guideline authors were unable to find guidelines on which professional groups should manage adults with CCMs. However, the authors recommend that any adult with a CCM should be seen by a neurologist or neurosurgeon with a vascular sub-specialty interest who can advise on the treatment of CCMs. Any adult with a CCM causing one or more epileptic seizures should be seen by an appropriate specialist, in keeping with epilepsy management guidelines (SIGN, 2005; NICE, 2012). Adults concerned about pre-symptomatic genetic testing should see a clinical geneticist prior to any testing being undertaken.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Cerebral cavernous malformations (CCM)

Guideline Category

Assessment of Therapeutic Effectiveness

Diagnosis

Management

Risk Assessment

Treatment

Clinical Specialty

Internal Medicine

Medical Genetics

Neurological Surgery

Neurology

Radiation Oncology

Radiology

Intended Users

Advanced Practice Nurses

Allied Health Personnel

Hospitals

Nurses

Patients

Physician Assistants

Physicians

Guideline Objective(s)

To provide guidelines for diagnosis and management of cerebral cavernous malformations (CCM) in adults

Target Population

Adults with cerebral cavernous malformations (CCM)

Interventions and Practices Considered

Diagnosis/Evaluation

1. Brain magnetic resonance imaging (MRI) using T1-weighted, T2-weighted, and hemosiderin-sensitive T2*/GRE sequences
2. Use of cerebral cavernous malformation (CCM) diagnostic criteria and definitions and reporting standards for CCM hemorrhage
3. Mutation analysis in the CCM 1, 2, and 3 genes

Treatment/Management

1. Treatment decisions made on a case-by-case basis
2. Management of first seizures and epilepsy using existing guidelines
3. Treatment of mothers with CCM before, during, and after birth
4. Antithrombotic or thrombolytic therapy
5. Neurosurgery
6. Stereotactic radiosurgery

Major Outcomes Considered

- Sensitivity and specificity of magnetic resonance imaging (MRI) in diagnosing cerebral cavernous malformations (CCM)
- Risk of future intracerebral hemorrhage or focal neurological deficit
- First seizure of epilepsy
- Functional outcome
- Frequency of genetic mutations or deletions in the CCM 1, 2, and 3 genes

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Identification of Questions

The guideline authors formulated specific management questions by consensus, using the PICO principle by specifying for each question: Patients (i.e., adults with cerebral cavernous malformations [CCM]), Intervention/Indicator, Comparator/Control, and the Outcome of interest. They identified important outcomes in discussion with the two patient support groups involved with the creation of these guidelines. They judged the relative importance of the outcomes, and prioritized death and new or worsened clinically symptomatic focal neurological deficits (FNDs) (whether or not new intracerebral hemorrhage [ICH] had been confirmed by imaging or pathological examination).

Literature Search

The guideline authors used electronic strategies (see Appendix 1 in the original guideline document) to search for journal articles about CCM published prior to 1 January 2011 and indexed in OVID Medline and EMBASE. Pairs of the group of three reviewers reviewed the titles and abstracts of eligible articles and excluded articles if: they were reviews and did not report original data, they did not address the specific management questions, they were exclusive to children with CCM, they reported fewer than 20 adults with CCM, the guideline authors were unable to extract relevant data from the article, or they were not designed to address the specific PICO questions (see Appendix 2 in the original guideline for the list of excluded studies and the reasons for their exclusion). If there were disagreements or uncertainties amongst the pair of reviewers, they were arbitrated by a third reviewer.

For diagnostic guidelines the search was limited to studies testing the accuracy of CCM diagnostic criteria applied to a consecutive series using a pathological reference standard and magnetic resonance imaging (MRI) as the index test.

For therapeutic guidelines the search was limited to studies of CCM treatment involving at least 20 adults that examined surgical resection and/or stereotactic radiosurgery, in which a group of adults receiving treatment was compared to either another group receiving a different treatment or to a conservatively-managed (untreated) group of adults. The guideline authors have stratified their specific management questions by adults' mode of clinical presentation because the future risks of hemorrhage from CCM may be higher if the CCM initially comes to medical attention with a hemorrhage (see Section 1.5 and Figure 2 in the original guideline document). The guideline authors sought to further stratify the answers to specific management questions by CCM location (because it too may influence the future risk of hemorrhage), and to distinguish outcomes for adults with solitary or multiple CCM.

For genetic guidelines the guideline authors sought studies of the frequency of genetic mutations or deletions in the CCM 1, 2, and 3 genes in three groups of adults with CCM: (1) adult with a single CCM but no family history, (2) adult with at least one CCM and a family history, and (3) adult with multiple CCMs but no family history. Papers included had completed analysis of at least one entire gene by a polymerase chain reaction (PCR)-mutation detection strategy, with or without deletion analysis by multiplex ligation-dependent probe amplification (MLPA). Papers with a risk of bias by inclusion of a significant Hispanic cohort were excluded.

Number of Source Documents

A total of 1769 articles were initially identified by the literature searches, and 204 full-text articles were assessed for eligibility. See Appendix 2 in

the original guideline document for the list of excluded studies and the reasons for their exclusion.

For diagnostic guidelines, one study met the inclusion criteria.

For therapeutic guidelines, the inclusion criteria were not met by any studies.

For genetic guidelines, 5 studies were included.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Not Given)

Rating Scheme for the Strength of the Evidence

The guideline authors used the Oxford Centre for Evidence-Based Medicine Levels of Evidence to grade the strength of the evidence (<http://www.cebm.net/ocebm-levels-of-evidence/>

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The guideline authors followed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group's recommendations for developing these guidelines, involving two separate processes of grading the quality of the evidence available and then grading the strength of each recommendation in the guidelines (www.gradeworkinggroup.org

Grading the Quality of the Evidence

Pairs of the group of three reviewers independently graded the quality of evidence available in each of the articles pertinent to diagnostic and therapeutic questions using the Centre for Evidence-Based Medicine (CEBM) Levels of Evidence published in 2011 (<http://www.cebm.net/ocebm-levels-of-evidence/>

For studies of diagnostic test accuracy, the guideline authors sought studies graded as Level 1 (systematic review of cross sectional studies with a consistently applied reference standard and blinding) or Level 2 (individual cross sectional studies with consistently applied reference standard and blinding). For studies of the benefits and harms of treatments, the authors sought studies graded as Level 1 (systematic review of randomized trials or n-of-1 trials) or Level 2 (randomized trial or observational study with dramatic effect). The guideline authors used a published definition of a dramatic effect in an observational treatment study, "a sufficiently extreme difference between the outcome ranges for treated and untreated patients might be defined by two rules: (a) that the conventionally calculated probability of the two groups of observations coming from the same population should be less than 0.01 and (b) that the estimate of the treatment effect (rate ratio) should be large... The guideline authors suggest that rate ratios beyond 10 are highly likely to reflect real treatment effects, even if confounding factors associated with the treatment may have contributed to the size of the observed associations." If there appeared to be a dramatic effect in an observational treatment study the guideline authors also judged whether the risk of bias in the study was high, and if it was the article was excluded (see Appendix 2 in the original guideline document). Three reviewers agreed on the overall quality of the evidence relevant to each Patient, Intervention/Indicator, Comparator/Control, and Outcome (PICO) question which was available after this selection process, and other members of the guidelines panel approved the final grading.

Two reviewers independently reviewed a selection of the articles that were identified as being potentially relevant to the genetic questions in these guidelines from the literature search (see Appendix 1 in the original guideline document). In the absence of CEBM criteria for grading the quality of the evidence in genetic testing studies, the reviewers identified articles that they thought best answered these questions.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The guideline authors followed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group's recommendations for developing these guidelines, involving two separate processes of grading the quality of the evidence available and then grading the strength of each recommendation in the guidelines (www.gradeworkinggroup.org).

Grading the Strength of Recommendations

After considering the grade of the quality of the evidence available for each Patient, Intervention/Indicator, Comparator/Control, and Outcome (PICO) question described in a document circulated electronically, the guidelines panel incorporated their judgments about the underlying values and preferences related to the management options and outcomes, the balance of desirable and undesirable effects, and the balance of net benefits and cost, culminating in a recommendation. In a consensus discussion, the guidelines panel felt unable to grade the strength of their recommendations in the light of the quality of the evidence available.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Not stated

Description of Method of Guideline Validation

Not applicable

Evidence Supporting the Recommendations

References Supporting the Recommendations

Al-Shahi Salman R, Hall JM, Horne MA, Moultrie F, Josephson CB, Bhattacharya JJ, Counsell CE, Murray GD, Papanastassiou V, Ritchie V, Roberts RC, Sellar RJ, Warlow CP, Scottish Audit of Intracranial Vascular Malformations (SAIVMs) collaborators. Untreated clinical course of cerebral cavernous malformations: a prospective, population-based cohort study. *Lancet Neurol*. 2012 Mar;11(3):217-24. [PubMed](#)

National Institute for Health and Clinical Excellence (NICE). The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Jan. 117 p. (Clinical guideline; no. 137).

Rigamonti D, Drayer BP, Johnson PC, Hadley MN, Zabramski J, Spetzler RF. The MRI appearance of cavernous malformations (angiomas). *J Neurosurg*. 1987 Oct;67(4):518-24. [PubMed](#)

Scottish Intercollegiate Guidelines Network (SIGN). Diagnosis and management of epilepsy in adults. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2005 Oct. 49 p. (SIGN publication; no. 70).

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Improved care and quality of life in people with cerebral cavernous malformations (CCM)

Potential Harms

For studies of the benefits and harms of treatments, the authors sought studies graded as Level 1 (systematic review of randomized trials or n-of-1 trials) or Level 2 (randomized trial or observational study with dramatic effect).

Qualifying Statements

Qualifying Statements

The guideline authors found few published studies of the diagnosis and treatment of cerebral cavernous malformations (CCMs) of level 1 or 2 quality according to the Centre for Evidence-Based Medicine's 2011 criteria (<http://www.cebm.net/ocebml-levels-of-evidence/>) , which enabled them to make few specific recommendations for the clinical investigation and management of adults with CCMs.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Patient Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012

Guideline Developer(s)

Cavernoma Alliance UK - Nonprofit Organization

Genetic Alliance UK - Nonprofit Organization

Source(s) of Funding

The creation of these guidelines was jointly funded by Cavernoma Alliance UK and a Facilitating Networks grant to Genetic Alliance UK.

Guideline Committee

Not stated

Composition of Group That Authored the Guideline

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Scientist Office of the Scottish Government Health Department, and Cavernoma Alliance UK. NS has received funding from the Medical Research Council and the Stroke Association. MP, KK, IS, CR, JB, and NK have not declared any competing interests.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the [Cavernoma Alliance UK Web site](#) .

Availability of Companion Documents

None available

Patient Resources

Information about cavernomas can be found on the [Cavernoma Alliance UK Web site](#) .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

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